EXTENDED RELEASE PHARMACEUTICAL COMPOSITIONS OF DIVALPROEX SODIUM

Technical Field of the Invention

The present invention relates to extended release formulations that include valproic acid, a pharmaceutically acceptable salt, ester, or amide thereof, or divalproex sodium, and processes for the preparation thereof.

Background of the Invention

Valproic acid, 2-propylpentanoic acid, and its derivatives are widely used in the treatment of mania, migraine and epilepsy. These compounds dissociate into the valproate ion in the gastrointestinal tract.

Valproic acid and its derivatives have a few physical characteristics that present problems when formulating into dosage forms. They are either liquid or liquefy rapidly and are sticky. Further, most of them are extremely hygroscopic in nature. These physicochemical properties of valproic acid and its derivatives pose serious problems during the manufacturing of the pharmaceutical compositions.

Additionally, valproic acid and its derivatives also suffer from relatively short elimination half-lives. For example, the half life of valproic acid has been reported at between 6 to17 hours in adults and 4 to14 hours in children. In order to maintain a reasonably stable plasma concentration, frequent dosing is required. This in turn results in an inconvenience for the patient and ultimately leads to poor compliance and a widely fluctuating plasma concentration.

U.S. Patent No. 6,419,953 describes an extended release matrix tablet comprising a valproate compound, hydroxypropyl methylcellulose, lactose, microcrystalline cellulose, and silicon dioxide having an average particle size ranging between about 1 micron and about 10 microns. The patent further teaches that addition of either 1% silicon dioxide or/and 5% microcrystalline cellulose to the hydrophilic matrix formulations of the invention doubles tablet hardness. However the problem of sticking still persists when conventionally used grades of silicon dioxide are employed, and can be overcome only by the use of a special grade of silicon dioxide (Syloid® 244) having a smaller average particle size ranging from about 1 micron to about 10 microns.

Summary of the Invention

In one general aspect there is provided an extended release pharmaceutical composition. The composition includes a drug capable of dissociating into a valproate ion, from about 15% to about 50% w/w of a high viscosity grade hydroxypropyl methylcellulose, and from about 0.1% to about 10% w/w of a low viscosity grade hydroxypropyl methylcellulose.

Embodiments of the pharmaceutical composition may include one or more of the following features. For example, the drug capable of dissociating into a valproate ion may be valproic acid and its pharmaceutically acceptable salts, esters, and amides. The valproic acid salt may be divalproex sodium and may be present from about 10% to about 90% by weight of the total pharmaceutical composition weight.

The pharmaceutical composition may be indicated for once a day dosing. The pharmaceutical composition may be a tablet or a capsule.

The high viscosity grade hydroxypropyl methylcellulose may be a high viscosity grade hydroxypropyl methylcellulose whose 2% aqueous solution has a nominal viscosity greater than about 10,000 cP or it may have a nominal viscosity from about 10,000 to about 100,000 cP. The high viscosity grade hydroxypropyl methylcellulose may be present from about 20% to about 40% by weight of the total pharmaceutical composition weight.

The low viscosity grade hydroxypropyl methylcellulose may be a low viscosity grade hydroxypropyl methylcellulose whose 2% aqueous solution has a nominal viscosity less than about 1,000 cP or the nominal viscosity comprises from about 5 to about 100 cP. The low viscosity grade hydroxypropyl methylcellulose may be present from about 1% to about 5% by weight of the total pharmaceutical composition weight.

The extended release pharmaceutical composition may further include one or more pharmaceutically inert excipients. The one or more pharmaceutically inert excipients may be one or more of glidants, lubricants, diluents and binders.

The extended release pharmaceutical composition may be free of microcrystalline cellulose.

In another general aspect there is provided a process for the preparation of an extended release pharmaceutical composition. The process includes blending a drug capable of dissociating into the valproate ion, from about 15% to about 50% w/w of a high viscosity grade hydroxypropyl methylcellulose and from about 0.1% to about 10% w/w of a low viscosity grade hydroxypropyl methylcellulose to form a blend; optionally granulating the blend; lubricating the blend; and compressing or filling into a suitable size solid dosage form.

Embodiments of the process may include one or more of the following features. For example, the drug capable of dissociating as valproate ion may be valproic acid and its pharmaceutically acceptable salts, esters, and amides or it may be divalproex sodium.

The pharmaceutical composition may be a tablet or a capsule.

The granulation may be carried out by wet granulation, dry granulation or melt extrusion.

In another general aspect there is provided a method of treating mania, migraine and epilepsy in a patient in need thereof. The method includes administering an extended release pharmaceutical composition which includes drug capable of dissociating into a valproate ion; from about 15% to about 50% w/w of a high viscosity grade hydroxypropyl methylcellulose; and from about 0.1% to about 10% w/w of a low viscosity grade hydroxypropyl methylcellulose.

Detailed Description of the Invention

The inventors have now developed a pharmaceutical composition for oral administration comprising a drug capable of dissociating to produce valproate ion, and a low and a high viscosity grade hydroxypropyl methylcellulose. The inventors have found that a low viscosity grade hydroxypropyl methylcellulose helps in maintaining the integrity of the matrix, thereby playing an important role in controlling the release of the drug from the matrix.

The extended release pharmaceutical composition releases the drug over a prolonged period of time in such a manner as to provide a sustained plasma concentration of the drug following once-a-day dosing.

The term 'pharmaceutical composition' as used herein includes all solid dosage forms including tablets, capsules, and pills. The tablets may be prepared by techniques known in the art and include a therapeutically useful amount of the valproate compound. One or more pharmaceutically acceptable excipients may be used as is necessary to form the tablet by such techniques. Tablets and pills may additionally be prepared with enteric coatings and other release-controlling coatings for the purpose of acid protection, easing swallowing ability, etc.

The term 'drug capable of dissociating into the valproate ion in the gastrointestinal tract' includes compounds that dissociate within the gastrointestinal tract to produce the valproate ion, including valproic acid, the sodium salt of valproate, divalproex sodium, any salt of valproic acid described below, and any of the prodrugs of valproic acid described below.

Valproic acid is known for its activity as an antiepileptic compound as described in the Physician Desk Reference, 52nd Edition, page 421, 1998. Upon oral ingestion within the gastrointestinal tract, the acid moiety dissociates to form a carboxylate moiety (i.e. a valproate ion).

The sodium salt of valproic acid is also known in the art as an anti-epileptic agent. It is also known as sodium valproate and is described in detail in The Merck Index, 12 Edition, page 1691, (1996).

Divalproex sodium (sodium hydrogen divalproate) is an effective antiepileptic agent and is also used for migraine and bipolar disorders. Similar to valproic acid, it also dissociates within the gastrointestinal tract to form the valproate ion. It is a stable co-ordination compound comprising of sodium valproate and valproic acid in a 1:1 ratio. It is formed during the partial neutralization of valproic acid with 0.5 equivalents of sodium hydroxide. The amount of drug may vary from about 10% to about 90% by weight of the total pharmaceutical composition weight.

In addition to these specific compounds, one of ordinary skill in the art would readily recognize that the carboxylic moiety of the valproate compound may be functionalized in a variety of ways. This includes forming compounds that readily metabolize in-vivo to produce valproate, such as valproate amide (valproimide), as well as

other pharmaceutically acceptable amides and esters of the acid (i.e. prodrugs). Also included are a variety of pharmaceutically acceptable salts.

Suitable pharmaceutically acceptable basic addition salts include cations based on alkali metals or alkaline earth metals, including lithium, sodium, potassium, calcium, magnesium and aluminum salts; nontoxic quaternary ammonia and amine cations including ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, diethylamine, and ethylamine. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, and piperazine.

Other possible compounds include pharmaceutically acceptable amides and esters. "Pharmaceutically acceptable ester" includes those esters that retain, upon hydrolysis of the ester bond, the biological effectiveness and properties of the carboxylic acid and are not biologically or otherwise undesirable. The alcohol component of the ester will generally comprise (i) a C_2 -C_{12} aliphatic alcohol that may include one or more double bonds and may include branched carbons; or (ii) a C_7 -C_{12} aromatic or heteroaromatic alcohols. This invention also contemplates the use of those compositions, which are both esters and at the same time are the pharmaceutically acceptable salts thereof.

"Pharmaceutically acceptable amide" refers to those amides that retain, upon hydrolysis of the amide bond, the biological effectiveness and properties of the carboxylic acid and are not biologically or otherwise undesirable. This invention also contemplates the use of those compositions, which are both amides as described herein, and at the same time are the pharmaceutically acceptable salts thereof.

The term 'extended release pharmaceutical composition' as used herein includes any pharmaceutical composition that achieves the slow release of a drug over an extended period of time, and includes both prolonged and controlled release compositions.

The term 'high viscosity grade hydroxypropyl methylcellulose' as used herein includes grades of hydroxypropyl methylcellulose whose 2% w/w aqueous solution has a nominal viscosity greater than about 10,000 cP.

The term 'low viscosity grade hydroxypropyl methylcellulose' as used herein includes grades of hydroxypropyl methylcellulose whose 2% w/w aqueous solution has a nominal viscosity less than about 1,000 cP.

Hydroxypropyl methylcellulose polymers which are hydrophilic in nature and of different viscosity grades may also be used, including those available under the brand name Methocel TM available from Dow Chemical Co. and Metolose from Shin Etsu Ltd. Examples of hydroxypropyl methylcellulose polymers having high viscosity include those available under the brand names Methocel K15M, Methocel K100M, Methocel E10M, Metolose 90SH 15000 and Metolose 90SH 39000 whose 2% by weight aqueous solution have viscosities of 15,000 cP, 100,000 cP 10,000 cP, 15,000 cP and 39,000 cP, respectively. The high viscosity grade of hydroxypropyl methylcellulose polymers may be used in the concentration range of about 15% to about 50% w/w, in particular about 20% to about 40% w/w.

The hydroxypropyl methylcellulose polymers of a low viscosity grade include those available under the brand names Methocel E5, Methocel E-15 LV, Methocel E50 LV, Methocel K100 LV Methocel F50 LV, Methocel E6LV, Methocel A15LV and Metolose 60SH 50, whose 2% by weight aqueous solutions have viscosities of 5 cP, 15 cP, 50 cP, 100 cP, 50 cP, 6cP, 15 cP, and 50 cP, respectively. The low viscosity grade of hydroxypropyl methylcellulose polymers may be used in the concentration range of about 0.1% to about 10% w/w, and in particular about 1% to about 5% w/w.

The extended release pharmaceutical composition may be prepared by processes known in the prior art including one or more of comminuting, mixing, granulation, melting, sizing, filling, drying, molding, immersing, coating, and compressing.

The extended release pharmaceutical composition may be prepared by wet granulation. The process includes blending a drug capable of dissociating as valproate ion in the gastrointestinal tract with one or more extended release polymers and optionally one or more pharmaceutically inert excipients; granulating the blend with a granulating fluid or solution/dispersion of binder; drying and sizing the granules; optionally blending with one or more pharmaceutically inert extragranular excipients; lubricating the granules/blend; compressing the lubricated blend/granules into suitably sized tablets; and optionally coating with one or more film forming polymers and coating additives.

The extended release pharmaceutical composition may also be prepared by dry granulation. The process includes blending a drug capable of dissociating into the valproate ion in the gastrointestinal tract with one or more extended release polymers and optionally one or more pharmaceutically inert excipients; dry granulating the blend by roller compactor or slugging; lubricating the granules/blend; compressing the lubricated blend/granules into suitably sized tablets; and optionally coating with one or more film forming polymer and coating additives.

The extended release pharmaceutical composition may also be prepared by direct compression. The process includes blending a drug capable of dissociating into the valproate ion in the gastrointestinal tract with one or more extended release polymers and optionally one or more pharmaceutically inert excipients; lubricating the blend; directly compressing the lubricated blend into suitably sized tablets; and optionally coating with one or more film forming polymers and coating additives.

The extended release pharmaceutical composition may be prepared by melt extrusion. The process includes blending a drug capable of dissociating into the valproate ion in the gastrointestinal tract with one or more extended release polymers and optionally one or more pharmaceutically inert excipients; melting the blend and then solidifying it into a compact mass; breaking the compact mass into granules; optionally blending with one or more pharmaceutically inert extragranular excipients; lubricating the granules/blend; compressing the lubricated granules/blend into suitably sized tablets; and optionally coating with one or more film forming polymers and coating additives.

The term "pharmaceutically acceptable inert excipients" as used herein includes all excipients used in the art of manufacturing solid dosage forms. Examples include one or more of binders, diluents, surfactants, lubricants/glidants, coloring agents, and mixtures thereof.

Suitable binders include one or more of methyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, gelatin, gum arabic, ethyl cellulose, polyvinyl alcohol, pullulan, pregelatinized starch, agar, tragacanth, sodium alginate, propylene glycol, and mixtures thereof.

Suitable diluents include one or more of calcium carbonate, calcium phosphate-dibasic, calcium phosphate-tribasic, calcium sulfate, cellulose-microcrystalline, cellulose

powdered, dextrates, dextrins, dextrose excipients, fructose, kaolin, lactitol, lactose, mannitol, sorbitol, starch, starch pregelatinized, sucrose, sugar compressible, sugar confectioners, and mixtures thereof.

Suitable surfactants include both non-ionic and ionic (cationic, anionic and zwitterionic) surfactants suitable for use in pharmaceutical dosage forms. These include polyethoxylated fatty acids and its derivatives, for example, polyethylene glycol 400 distearate, polyethylene glycol – 20 dioleate, polyethylene glycol 4 –150 mono dilaurate, polyethylene glycol –20 glyceryl stearate; alcohol – oil transesterification products, for example, polyethylene glycol – 6 corn oil; polyglycerized fatty acids, for example, polyglyceryl – 6 pentaoleate; propylene glycol fatty acid esters, for example, propylene glycol monocaprylate; mono and diglycerides for example glyceryl ricinoleate; sterol and sterol derivatives; sorbitan fatty acid esters and its derivatives, for example, polyethylene glycol – 20 sorbitan monooleate, sorbitan monolaurate; polyethylene glycol alkyl ether or phenols, for example, polyethylene glycol – 20 cetyl ether, polyethylene glycol – 10 – 100 nonyl phenol; sugar esters, for example sucrose monopalmitate; polyoxyethylene – polyoxypropylene block copolymers known as "poloxamer"; ionic surfactants, for example sodium caproate, sodium glycocholate, soy lecithin, sodium stearyl fumarate, propylene glycol alginate, octyl sulfosuccinate disodium, palmitoyl carnitine; and the like.

Suitable lubricants/glidants include one or more of colloidal silicon dioxide, stearic acid, magnesium stearate, calcium stearate, talc, hydrogenated castor oil, sucrose esters of fatty acid, microcrystalline wax, yellow beeswax, white beeswax, and mixtures thereof.

Suitable coloring agents include any FDA approved colors for oral use.

The pharmaceutical composition may optionally be coated with functional and/or non-functional layers comprising film-forming polymers, if desired.

Suitable film-forming polymers include one or more of ethylcellulose, hydroxypropyl methylcellulose, hydroxypropylcellulose, methylcellulose, carboxymethyl cellulose, hydroxymethylcellulose, hydroxyethylcellulose, cellulose acetate, hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, cellulose acetate trimellitate; waxes, such as, polyethylene glycol; methacrylic acid polymers, such as, Eudragit ® RL and RS; and mixtures thereof. Alternatively, commercially available

coating compositions comprising film-forming polymers marketed under various trade names, such as Opadry®, may also be used for coating.

The invention is further illustrated by the following examples, which are for illustrative purposes only and should not be considered as limiting the scope of the invention in any way.

EXAMPLE 1

Divalproex sodium, lactose, Methocel K-15M CR and Methocel E-5 were blended in a rapid mixer granulator. The granules were prepared by adding a granulation fluid (purified water) to the mixture of drug/polymer/lactose. The resulting granules were dried in a fluidized bed drier and sieved through suitable sieves. The dried granules were blended with talc, colloidal silicon dioxide and magnesium stearate and compressed into suitable sized tablets and coated with an aqueous dispersion of PEG 400 and Opadry.

Table 1: Composition of extended release tablets of divalproex sodium.

Ingredients	**Wt/tablet (mg) Example 1**
Divalproex sodium	542.3
Lactose	90.0
Methocel K-15M CR	320.0
Methocel E-5	20.0
Water	q.s.
Magnesium Stearate	5.0
Talc	8.0
Colloidal Silicon Dioxide	17.0

***In vitro* dissolution study**

An *In vitro* dissolution study of the extended release tablets of divalproex sodium as per composition of Example 1 was done in 900 ml phosphate buffer (pH 6.8) with 1% sodium lauryl sulphate in USP type II apparatus at a paddle speed of 100 rpm. The tablets were kept in sinker basket of 10#. The results are shown in Table 2.

Table 2: Drug release profile of extended release formulation.

Time (hr)	Cumulative percentage of drug released from the formulation of Example 1
1	16
2	27
4	35
8	53
12	69
16	78
20	92
24	102

While a particular formulation has been described above, it will be apparent that various modifications and combinations of the formulations detailed in the text can be made without departing from the spirit and scope of the invention. For example, the concentrations of high viscosity grade and low viscosity grade polymers may be varied as exemplified in Table 3.

Table 3: Composition of extended release tablets of divalproex sodium.

Ingredients	Wt/tablet (mg) Example 2	Wt/tablet (mg) Example 3	Wt/tablet (mg) Example 4
Divalproex sodium	542.3	542.3	538.1
Lactose	90.0	90.0	68.6
Methocel K-15M CR	310.0	330.0	360.0
Methocel E-5	30.0	12.0	8.0
Water	q.s.	q.s.	q.s.
Magnesium Stearate	5.0	5.0	3.0
Talc	8.0	8.0	7.3
Colloidal Silicon Dioxide	17.0	17.0	15.0

The following example describes a formulation which includes Divalproex sodium equivalent to 750 mg of valproic acid using the process described in Example 1.

EXAMPLE 5

Ingredients	**Wt/tablet (mg) Example 5**
Divalproex sodium	807.15
Lactose	18.90
Methocel K-100 MCR	254.0
Methocel E-5	6.0
Water	q.s.
Magnesium Stearate	3.0
Talc	10.95
Colloidal Silicon Dioxide	22.5

The extended release tablet formulations of the present invention thus provide an effective delivery system for once daily administration of valproic acid (divalproex sodium) to patients in need of such treatment.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are included within the scope of the present invention.